"Rheumatoid Arthritis: A Comprehensive Overview of Pathogenesis, Diagnosis, and Treatment"

Benito Johnson. D*., Essly Selva Jasmine. P., Santha Kumar. S., Madhuranthagan. M

Department of Pharmacology, RVS College of Pharmaceutical Sciences, Sulur, Coimbatore

***Corresponding Author**

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a systemic, autoimmune disease characterized by chronic synovial inflammation, progressive joint destruction, and multiple systemic manifestations. Affecting approximately 1% of the global adult population, RA significantly contributes to disability, morbidity, and economic burden.

Objective: This review outlines the current understanding of RA pathogenesis, diagnostic approaches, and therapeutic strategies, while highlighting emerging insights and treatment gaps.

Methods: A comprehensive overview was conducted based on current literature detailing the immunological, genetic, and environmental factors contributing to RA, as well as established and emerging treatment modalities.

Results: RA pathophysiology involves immune cell infiltration, synovial hyperplasia (pannus formation), neovascularization, and the production of inflammatory cytokines (TNF-α, IL-1, IL-6), matrix metalloproteinases, and autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies (ACPA). Genetic predisposition (notably HLA-DR4/DR1) interacts with environmental triggers (e.g., smoking, periodontitis, microbiome dysbiosis) to initiate autoimmunity. Diagnosis is supported by clinical evaluation, serological markers, and imaging modalities such as ultrasound and MRI. Early intervention using nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs)—including methotrexate and biologics—is critical for improving outcomes. Surgical management is reserved for end-stage disease.

Conclusion: Although current treatments can reduce symptoms and slow disease progression, they remain largely palliative and carry the risk of adverse effects. A deeper understanding of molecular and immunological mechanisms is paving the way for more targeted, effective, and safer therapies. Continued research is essential to optimize personalized treatment strategies and improve long-term outcomes in RA patients.

Keywords: Rheumatoid arthritis, Autoimmune disease, Synovitis, DMARDs, Methotrexate, Biologics, Inflammation, Immunopathology, ACPA, HLA-DR.

INTRODUCTION

Rheumatoid arthritis is a prevalent autoimmune disorder linked to increasing disability, systemic complications, premature mortality, and economic burdens. This condition is marked by inflammation and hyperplasia of the synovial membrane (commonly referred to as "swelling"), the production of autoantibodies (such as rheumatoid factor and anti–citrullinated protein antibody [ACPA]), destruction of cartilage and bone (leading to "deformity"), and various systemic manifestations, which encompass cardiovascular, pulmonary, psychological, and skeletal issues [1]. Another common manifestation of RA is morning stiffness in the impacted joints that persists for over 30 minutes, accompanied by fatigue, fever, weight loss, tender and swollen joints, warmth, and rheumatoid nodules located under the skin [2]. Rheumatoid Arthritis (RA) impacts 1% of the adult population and serves as a major factor in disability. The estimated global prevalence in Italy is approximately 0.5%. The

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underlying mechanisms of RA are not completely understood. Those who are genetically predisposed to this condition may develop it due to interactions with several environmental influences, including smoking habits[3].

Rheumatoid arthritis (RA) is classified as a polyarthritis, meaning it affects multiple joints (six or more). In the initial phases of the condition, it may only impact one or a few joints. Almost all peripheral joints are susceptible to the disease; nevertheless, the joints most frequently affected include those in the hands, feet, and knees, while the distal interphalangeal joints are typically preserved[4].

A variety of arthritis types have been studied and categorized to distinguish between non-inflammatory arthritis (osteoarthritis) and inflammatory arthritis resulting from crystal deposits (such as pseudogout, basic calcium phosphate disease, and gout), as well as those caused by bacterial and viral infections (including Staphylococcus aureus, Neisseria gonorrhea, complications from Lyme disease, Parvovirus, and Enterovirus) or by autoimmune mechanisms[5].

The fundamental pathological processes that cause arthritis vary depending on the specific type of arthritis involved. Nevertheless, irrespective of the type, these processes ultimately lead to harm to the joint tissues and cartilage, encompassing the synovium and bone. Although numerous biomolecular mechanisms have been proposed, the precise cause of RA is still not fully comprehended. A dominant hypothesis indicates that dysregulated citrullination leads to the production of anti-citrullinated protein antibodies (ACPAs)[6].

RA transplantation consists of three phases: the pre-transplant assessment, during which the patient's eligibility is evaluated; the transplantation phase, which involves the surgical replacement of damaged organs or tissues; and the post-transplant care phase, which includes monitoring for graft acceptance, managing immunosuppressive therapy, and supporting recovery. Each phase is crucial for enhancing outcomes and addressing issues associated with RA.

The "Bermuda triangle" of genetic, environmental factors, and autoimmunity initiates and sustains synovitis associated with RA [2–10]. Timely diagnosis and prompt, effective treatment are essential to avert joint damage, functional impairment, and adverse disease progression. Optimal RA management should occur within 3–6 months following disease onset; thus, there exists a limited "window of opportunity" to attain remission.

Although there is a comprehension of the pathophysiology of RA in relation to disease progression, the existing clinical treatment alternatives, including disease-modifying anti-rheumatic drugs (DMARDs), biologics, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs), offer merely palliative care. These treatments also lead to negative side effects, such as off-target multi-organ toxicity and an increased risk of infections[7].

The objectives of rheumatoid arthritis (RA) treatment are to alleviate joint inflammation and pain, enhance joint functionality, and avert joint damage and deformity. Treatment plans typically involve a mix of medications, weight-bearing exercises, patient education regarding the condition, and periods of rest. These treatments are usually tailored to meet the individual needs of each patient and are influenced by their general health status. This encompasses elements such as the progression of the disease, the specific joints affected, the patient's age, overall health, occupation, adherence to treatment, and understanding of the disease. This review briefly highlights the classic and current treatment options available to address the discomfort/complications of RA.

Types of rheumatoid arthritis:

1. Adult Rheumatoid Arthritis: it’s occurs between 25 and 50 years of age. It’s affects women three times more than men.

2. Juvenile Rheumatoid Arthritis (Still’s Disease): it’s occurring before 7 years of age.

3. Osteoarthritis: Second most frequent type of arthritis. This type affects the hyaline cartilage in weight bearing joints. Usually occurs because of destruction of bone coverings at the joints due to repeated use or trauma.

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4. Ankylosing Spondylitis: Most prevalent in males with the age of onset ranging from 20 to 40 years of age. It affects he axial skeleton and large peripheral joints of the body. Common symptoms include recurrent back pain and early morning stiffness.

Pathophysiology Of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is marked by the infiltration of T cells, B cells, and monocytes into the synovial membrane across various joints. This infiltration is preceded by the activation of endothelial cells; neovascularization, which is the formation of new blood vessels, is another defining feature of RA synovitis. The proliferation of synovial fibroblast-like and macrophage-like cells results in a hyperplastic layer of the synovial lining. This thickened synovial membrane, commonly referred to as 'pannus,' encroaches upon the periarticular bone at the junction of cartilage and bone, causing bony erosions and degradation of cartilage[5].

Recent studies highlight oxidative stress as a key element in the pathophysiology of rheumatoid arthritis, exacerbating inflammatory processes and causing tissue damage through the excessive generation of reactive oxygen species (ROS) and weakened antioxidant defenses[8]. In the synovial fluid the presence of neutrophils has been reported, which produce proteases and reactive oxygen species (ROS) that may cause bone erosion and cartilage degradation[5].

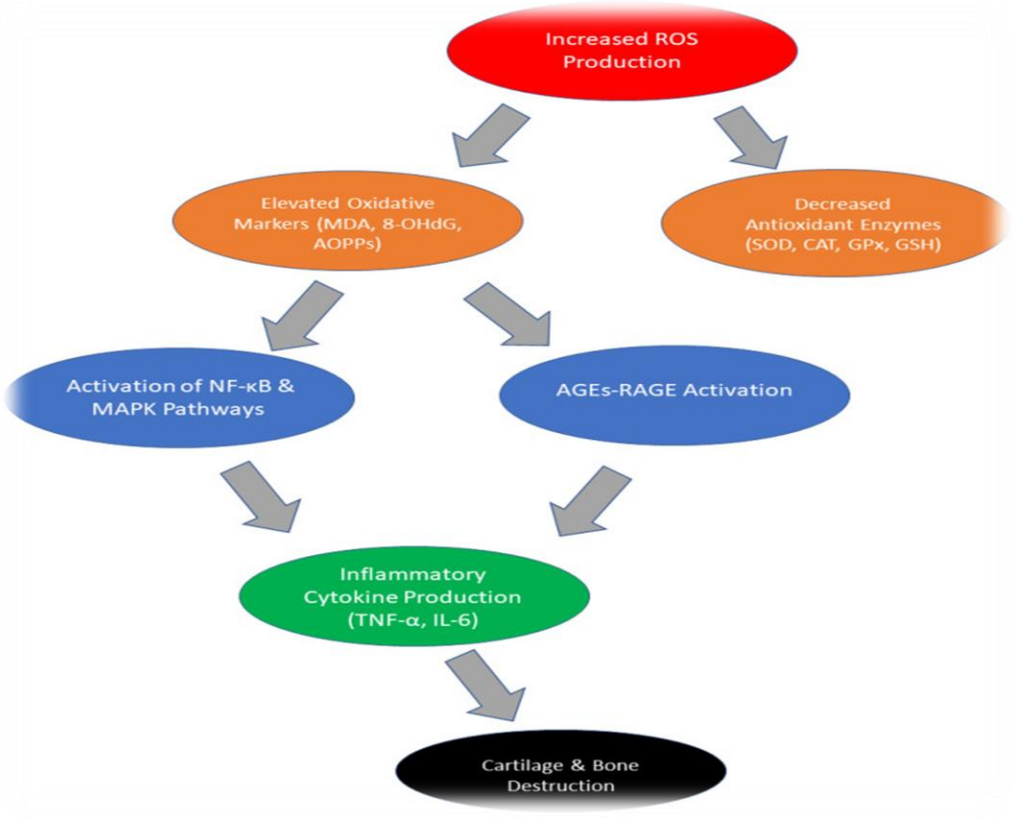

Figure 1: Pathophysiological changes in RA patients due to oxidative stress

The causes of RA are complex and involve a combination of genetic and environmental influences. A significant factor is genetic predisposition, especially the presence of certain HLA-DR4 and HLA-DR1 alleles, which increase the risk of developing the disease[9]. Environmental risk factors associated with RA include smoking, periodontitis, and the characteristics of the gut, mouth, and lung microbiomes, along with viral infections[10]. In terms of the microbiome, Prevotella species, which are found in increased numbers in the gastrointestinal tract during early RA, and Porphyromonas gingivalis, linked to periodontitis, may contribute to the disease's pathogenesis[11]. Recent findings indicate that bacteria could migrate from the gut to other tissues, leading to inflammation and autoimmunity[12]. The connection between genetics and environmental factors is highlighted by recent studies showing that HLA-DR molecules in RA patients present peptides of autoantigens that share sequence homology with epitopes from proteins of commensal bacterial species found in RA.

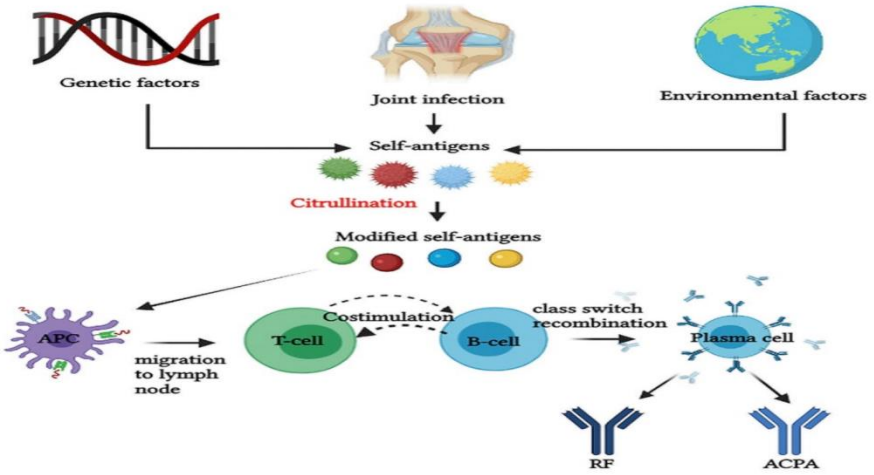

Figure 2. Immunological processes in the pre-RA phase. ACPA, anti-citrullinated protein antibodies; APC, antigen-presenting cells; RF, rheumatoid factor.

Immunological processes are crucial for comprehending the initiation and development of RA. CD4+ T lymphocytes are pivotal in triggering immune responses through the secretion of cytokines like interleukin-17 (IL-17) and interferon gamma (IFN-γ). These cytokines facilitate the attraction of inflammatory cells, such as macrophages and neutrophils, which invade the synovial membrane and sustain inflammation[13]. In cases of synovitis lesions, lymphocytes and synoviocytes generate significant quantities of inflammatory cytokines, including TNF, interleukin (IL)-1, and IL-6, which contribute to the development of synovitis. Alongside systemic manifestations such as low-grade fever and malaise, there is frequently extra-articular organ involvement, which may include conditions like kerato conjunctivitis sicca, sialadenitis, and interstitial pneumonia. Moreover, synoviocytes stimulated by cytokines produce matrix metalloproteinases (MMP), which are subsequently released into the synovial fluid. These enzymes lead to the degradation and absorption of cartilage. Additionally, both synoviocytes and lymphocytes express receptor activator of nuclear factor-kappa B ligand (RANKL), which facilitates the maturation and activation of osteoclasts. Inflammatory granulation tissues, characterized by proliferative and stratified synoviocytes, expand until they make contact with the bones. Multinucleated osteoclasts then proceed to destroy and absorb bone, resulting in joint destruction, particularly at the sites of contact.

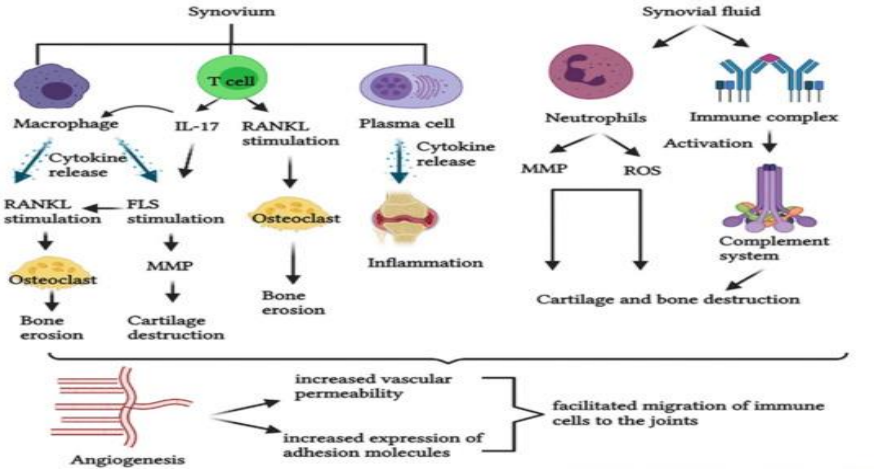

Figure 3. Pathological mechanisms in RA. IL, interleukin; FLS, fibroblast-like synoviocytes; MMP, matrix metalloproteinase; RANKL, receptor activator of nuclear factor-kB ligand; ROS, reactive oxygen species.

The initial abrasions observed in rheumatoid synovitis appear to be due to microvascular damage, accompanied by an increase in synovial lining cells, which can be seen laterally with perimysial infiltration of mononuclear cells. Microscopic examination reveals distinct characteristic features, such as hyperplasia and hypertrophy of the cells within the synovial lining. The primary or sectional variations in vascular changes include embolism, ventricular damage, and the formation of new blood vessels in areas with compromised blood supply due to

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trauma, as well as dropsy and infiltration by mononuclear cells, including lymphocytes, monocytes, and immature granulocytes. The endothelial cells of the rheumatoid synovium exhibit high endothelial venules typical of lymphoid organs. This condition is modified by cytokine exposure, which enhances the infiltration of cells into the tissues, leading to a continuous increase in the number of linkage molecules involved in this process. The size and composition of the mononuclear cells may differ depending on the collections[14].

Diagnosis Of Rheumatiod Arthiritis:

There is currently no definitive test for diagnosing rheumatoid arthritis (RA). Until now, the revised criteria established by the ACR in 1987 have been used for RA diagnosis. Recently, new criteria have been introduced to distinguish between patients who are likely to progress to RA (based on the 1987 ACR criteria) and those who are not. The purpose of these new criteria is to facilitate the early identification of individuals with high-risk early inflammatory arthritis for treatment, thereby preventing the onset of an arthritic condition that meets the 1987 criteria. These criteria offer valuable information for initiating treatment sooner and allow for a quicker implementation of DMARDs therapy.[15]

Both ultrasound and MRI are recommended for the diagnosis and monitoring of disease activity in patients with RA. High-resolution musculoskeletal ultrasound allows for the imaging of inflamed joints, showcasing synovial proliferation through grayscale imaging, as well as detecting active inflammation and neoangiogenesis via power Doppler. Furthermore, ultrasound can identify bone erosions and subclinical synovitis, which may lead to radiographic disease progression, even when the patient appears to be in clinical remission. Because of these capabilities, ultrasound is extensively utilized in both clinical practice and clinical trials for diagnosing RA and monitoring disease states.[16]

Treatment Of Rheumatiod Arthiris

Once RA is diagnosed in a patient, the overall treatment target is to either reach full remission or at least significantly lower disease activity within a span of approximately 6 months in order to prevent joint damage, disability, and systemic manifestations of RA [7,129]. The importance of prompt and targeted RA treatment is underlined by the fact that 80% of insufficiently treated patients will have misaligned joints and 40% of patients will be unable to work within 10 years of disease onset.[16]

It is the clinician's task to address the patient's pain, swelling, and stiffness with effective interventions. There are three modalities that every clinician should address in early RA: (1) analgesics, (2) corticosteroids, and (3) DMARDs.[17]

There are special considerations for women of childbearing age because many medications have deleterious effects on pregnancy. Goals of therapy include minimizing joint pain and swelling, preventing deformity (such as ulnar deviation) and radiographic damage (such as erosions), maintaining quality of life (personal and work), and controlling extra-articular manifestations. Disease modifying anti-rheumatic drugs (DMARDs) are the mainstay of RA therapy.[18]

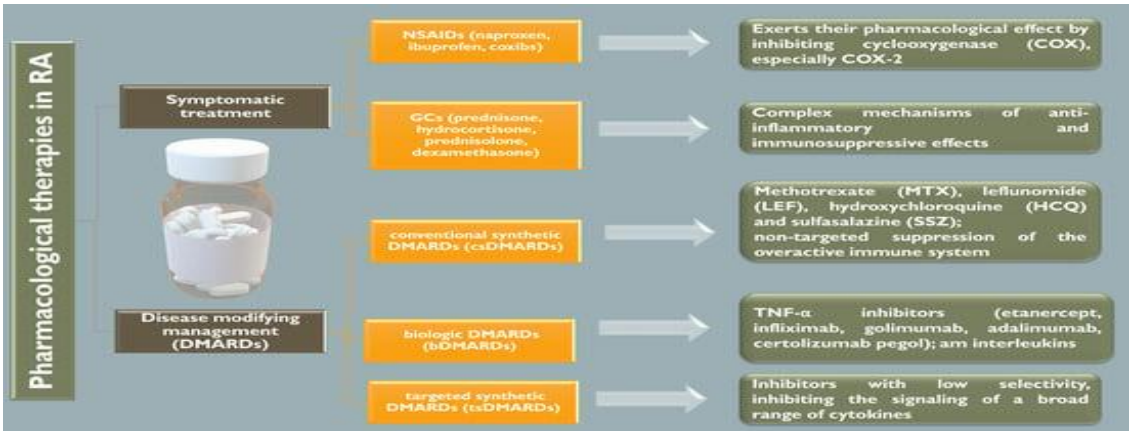

Fig 4: Pharmacological Therapies in Ra

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First-Line Management: Non-Steroidal Anti-Inflammatory Drugs and Corticosteroids:

The primary objective of first-line treatment is to alleviate pain and reduce inflammation. Fast-acting medications include nonsteroidal anti-inflammatory drugs (NSAIDs) such as acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and etodolac (Lodine). Aspirin serves as an effective anti-inflammatory for rheumatoid arthritis (RA) when administered in high doses, as it inhibits prostaglandins. It is among the oldest NSAIDs utilized for joint pain. High doses of aspirin may lead to side effects such as tinnitus, hearing loss, and gastric intolerance. There are newer NSAIDs available that are equally effective as aspirin and require fewer daily doses. NSAIDs function by inhibiting cyclo-oxygenase, thereby preventing the production of prostaglandins, prostacyclin, and thromboxanes. Common side effects include nausea, abdominal pain, ulcers, and gastrointestinal (GI) bleeding. These adverse effects can be mitigated by taking the medication with food, antacids, proton pump inhibitors, or misoprostol (Cytotec). A more recent NSAID, celecoxib (Celebrex), is a selective Cox-2 inhibitor that poses a lower risk of GI side effects.[19]

Corticosteroids are more effective anti-inflammatory medications compared to NSAIDs, but they also have more significant side effects. Consequently, they are recommended only for short durations at low doses, particularly during RA exacerbations or flares. Intra-articular corticosteroid injections can address localized inflammation symptoms.[20] These medications function by inhibiting the release of phospholipids and reducing eosinophil activity, which in turn lessens inflammation. Potential side effects include bone density loss, weight gain, diabetes, and immunosuppression. To mitigate bone thinning, it is advisable for patients to take calcium and vitamin D supplements. Additionally, tapering doses gradually as the patient's condition improves can help minimize side effects. It is crucial not to abruptly stop corticosteroid treatment, whether injected or oral, as this may result in suppression of the hypothalamic-pituitary-adrenal axis (HPA) or trigger RA flares.[21]

Second-Line Management: Medications that Modify Disease Progression in Rheumatology

The primary objective of second-line treatment is to encourage remission by decelerating or halting the advancement of joint damage and deformity. Medications are regarded as slow-acting since they require several weeks to months to show effectiveness. Disease-modifying antirheumatic drugs (DMARDs) can also lower the likelihood of developing lymphoma, which may be linked to RA.

Methotrexate (MTX) serves as the primary second-line medication, often referred to as an anchor drug. It acts as a folic acid analog, competitively blocking the binding of dihydrofolic acid (FH2) to the enzyme that converts FH2 into folinic acid (FH4). The absence of FH4 disrupts the metabolism of purine and pyrimidine, inhibiting the synthesis of amino acids and polyamines. As an immunosuppressive agent, MTX necessitates regular blood monitoring due to potential side effects, including liver issues, cirrhosis, and bone marrow damage. Supplementing with folic acid may help mitigate these side effects. MTX is recognized as an effective DMARD, exhibiting a lower frequency of side effects compared to other DMARDs, and offers dosage flexibility, allowing for adjustments as required. To date, substantial evidence supports the advantages of combining conventional synthetic DMARDs over MTX monotherapy. Nevertheless, combinations of biological and synthetic DMARDs are reported to outperform MTX, albeit with increased side effects and higher costs.[22]

Hydroxychloroquine (Plaquenil) is an antimalarial medication that can be utilized for the long-term management of rheumatoid arthritis (RA). This drug reduces the release of proinflammatory cytokines derived from monocytes. Common adverse effects include gastrointestinal issues, skin reactions, and central nervous system disturbances. Notably, high doses of this medication can impact the eyes, necessitating regular consultations with an ophthalmologist for patients on this treatment[23].

Sulfasalazine (Azulfidine) is a DMARD primarily employed in treating irritable bowel disease. When combined with anti-inflammatory drugs, it can also be effective for RA. The precise mechanism by which this drug operates in RA treatment remains unclear. It is believed that sulfapyridine, a metabolite formed after administration, may lower the secretion of interleukin (IL)-8 and monocyte chemoattractant protein (MCP). This medication is associated with gastrointestinal and central nervous system side effects, as well as the potential for rashes.[24]

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Gold salts, including aurothioglucose (Solganal), auranofin (Ridaura), gold sodium thiomalate (Myochrysine), and D-penicillamine (Depen and Cuprimine), have been commonly utilized in the management of RA. These DMARDs necessitate regular blood and urine examinations due to potential harm to the bone marrow and kidneys. Their use has declined recently in favor of more effective therapies, especially MTX. Other immunosuppressive drugs such as azathioprine (Imuran), cyclophosphamide (Cytoxan), chlorambucil (Leukeran), and cyclosporine (Sandimmune) may be used, but they are generally reserved for patients experiencing very aggressive RA or complications associated with the disease.[25]

Newer medications

Abatacept (Orencia) is a biologic drug that functions by inhibiting T cell activation. It is administered as an intravenous infusion once a month or as a subcutaneous injection once a week. This medication is intended for patients who have not responded adequately to conventional DMARDs[26]. Tocilizumab (Actemra) is another biologic that operates by blocking IL-6, a key inflammatory messenger. It is given through intravenous infusion on a monthly basis or through weekly subcutaneous injections. This treatment is also for patients who have not been effectively managed with traditional DMARDs [27].

Surgery;

Joint surgery for individuals with RA peaked in the 1990s. Nevertheless, a study conducted in 2010 revealed a decline in joint surgery rates among RA patients aged 40 to 59 years. Conversely, those over 60 years experienced an increase in surgery rates[28]. Surgery is considered a last resort for treating RA. It is indicated in cases of persistent joint pain or functional decline resulting from joint damage after all nonsurgical methods have been exhausted. At this stage, the disease is deemed 'end-stage.' The primary aim of surgical intervention is to alleviate the patient's pain and restore joint functionality. Patients requiring surgical treatment should be assessed according to their individual needs, as there are various types of surgical procedures available. A tenosynovectomy entails the removal of inflamed tendon sheaths or the repair of a recent tendon tear, most frequently in the hand[29]. Radiosynovectomy serves as an alternative to surgical synovectomy; it involves the intra-articular injection of small radioactive particles, is cost-effective, and can address multiple joints at once[30]. Torn tendons can also be repaired through arthroscopy, particularly in the rotator cuff of the shoulder. The excision of inflamed synovium via arthroscopy or open synovectomy has become less common due to the emergence of more effective alternatives. Another surgical option is osteotomy, where weight-bearing bones are realigned to correct valgus or varus deformities, most often in the knee[31]. Joint fusion may be performed to stabilize joints that cannot be easily replaced, such as the ankle, wrist, thumb, and cervical spine. A soft-tissue release procedure can be conducted to rectify severe contractures around joints that limit the range of motion; however, this is an older technique that is not frequently employed [32].

Other therapy:

It has been found that, in contrast to suggestions in the past, there are no specific foods that patients with RA should avoid. The idea that diet can “aggravate” symptoms is no longer accepted as true [33]. Home remedies have been proven to be helpful for patients suffering from RA, although they are not as effective as DMARDs. Fish oils and omega-3 fatty acid supplements are beneficial for the short-term symptoms of RA. Cumin has been shown to exhibit anti-inflammatory properties in individuals suffering from this disease. Supplementation with calcium and vitamin D may be beneficial in averting osteoporosis. Finally, folic acid can assist in mitigating the adverse effects of MTX [34] Finally, due to scientific progress and a deeper understanding of molecular mechanisms, we can expect newer and improved treatment options to emerge soon[35].

CONCLUSION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that significantly affects the quality of life, leading to joint destruction, disability, and systemic complications. Its pathogenesis is complex, involving genetic predisposition, environmental factors (such as smoking and microbiome imbalances), and autoimmune responses, including the production of autoantibodies like ACPA and RF. Central to its pathology is synovial

inflammation, oxidative stress, and immune-mediated damage, resulting in cartilage degradation and bone erosion.

Timely diagnosis and early intervention within the "window of opportunity" (typically within 3–6 months of onset) are crucial for preventing irreversible joint damage and disability. Despite advances in diagnostic tools, including imaging techniques like ultrasound and MRI, there is no single definitive test for RA, making clinical assessment essential.

Treatment strategies focus on relieving symptoms, preserving joint function, and halting disease progression. While NSAIDs and corticosteroids provide symptomatic relief, disease-modifying anti-rheumatic drugs (DMARDs), particularly methotrexate, remain the cornerstone of long-term therapy. Biologics and targeted synthetic DMARDs offer additional options for refractory cases, albeit with higher costs and risks. Surgical interventions are reserved for end-stage disease when conservative treatments fail.

Alternative therapies, nutritional supplements, and lifestyle modifications may support symptom management but cannot replace pharmacologic treatment. Continuous advancements in understanding RA's molecular and immunological underpinnings are likely to yield more targeted and effective therapies in the future.

Overall, managing RA requires a personalized, multidisciplinary approach that includes early diagnosis, aggressive treatment, regular monitoring, and patient education to optimize outcomes and improve the quality of life for those affected.

REFERENCES

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. New England Journal of Medicine. 2011 Dec 8;365(23):2205-19.
2. Bullock J, Rizvi SA, Saleh AM, Ahmed SS, Do DP, Ansari RA, Ahmed J. Rheumatoid arthritis: a brief overview of the treatment. Medical Principles and Practice. 2019 Mar 1;27(6):501-7.
3. Parisi S, Ditto MC, Ghellere F, Panaro S, Piccione F, Borrelli R, Fusaro E. Update on tocilizumab in rheumatoid arthritis: a narrative review. Frontiers in Immunology. 2025 Feb 24;16:1470488.
4. Smolen JS, Steiner G. Therapeutic strategies for rheumatoid arthritis. Nature reviews Drug discovery. 2003 Jun 1;2(6):473-88.
5. Radu AF, Bungau SG. Management of rheumatoid arthritis: an overview. Cells. 2021 Oct 23;10(11):2857.
6. Kurowska, W.; Kuca-Warnawin, E.H.; Radzikowska, A.; Ma´sli ´nski, W. The role of anti-citrullinated protein antibodies (ACPA) in the pathogenesis of rheumatoid arthritis. Cent. J. Immunol. 2017, 42, 390–398
7. Thangadurai M, Sethuraman S, Subramanian A. Drug Delivery Approaches for Rheumatoid Arthritis: Recent Advances and Clinical Translation Aspects. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2025;42(3).
8. Bilski R, Nuszkiewicz J. Antioxidant Therapies as Emerging Adjuncts in Rheumatoid Arthritis: Targeting Oxidative Stress to Enhance Treatment Outcomes. International Journal of Molecular Sciences. 2025 Mar 21;26(7):2873.
9. Kapitány A, Zilahi E, Szántó S, SZüCS G, Szabó Z, Végvári A, Rass P, Sipka S, Szegedi G, Szekanecz Z. Association of Rheumatoid Arthritis with HLA-DR1 and HLA-DR4 in Hungary. Annals of the New York Academy of Sciences. 2005 Jun;1051(1):263-70.
10. Tan EM, Smolen JS. Historical observations contributing insights on etiopathogenesis of rheumatoid arthritis and role of rheumatoid factor. J Exp Med. 2016;213(10):1937-1950.
11. Wegner N, Wait R, Sroka A, et al. Peptidylarginine deiminase from Porphyromonas gingivalis citrullinates human fibrinogen and α-enolase: implications for autoimmunity in rheumatoid arthritis. Arthritis Rheum. 2010;62(9): 2662-2672
12. Manfredo Vieira S, Hiltensperger M, Kumar V, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. Science. 2018; 359(6380):1156-1161
13. Jang S, Kwon EJ, Lee JJ. Rheumatoid arthritis: pathogenic roles of diverse immune cells. International journal of molecular sciences. 2022 Jan 14;23(2):905.

14. Nithyashree RS, Deveswaran R. A comprehensive review on rheumatoid arthritis.
15. Heidari B. Rheumatoid Arthritis: Early diagnosis and treatment outcomes. Caspian journal of internal medicine. 2011;2(1):161.
16. Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020 Apr 3;9(4):880.
17. Cush JJ. Rheumatoid arthritis: early diagnosis and treatment. The Medical Clinics of North America. 2021 Mar 1;105(2):355-65.
18. Wasserman AM. Diagnosis and management of rheumatoid arthritis. American family physician. 2011 Dec 1;84(11):1245-52.
19. Ong CK, Lirk P, Tan CH, Seymour RA. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical medicine & research. 2007 Mar 1;5(1):19-34.
20. Combe B, Landewe R, Daien CI, Hua C, Aletaha D, Álvaro-Gracia JM, Bakkers M, Brodin N, Burmester GR, Codreanu C, Conway R. 2016 update of the EULAR recommendations for the management of early arthritis. Annals of the rheumatic diseases. 2017 Jun 1;76(6):948-59.
21. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, Brown JP. Cohen. A. and Kim, H. (2013). A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy, Asthma and Clinical Immunology.;9(1):30-54.
22. Bullock J, Rizvi SA, Saleh AM, Ahmed SS, Do DP, Ansari RA, Ahmed J. Rheumatoid arthritis: a brief overview of the treatment. Medical Principles and Practice. 2019 Mar 1;27(6):501-7.
23. Silva JC, Mariz HA, Rocha LF, Oliveira PS, Dantas AT, Duarte AL, Pitta ID, Galdino SL, Pitta MG. Hydroxychloroquine decreases Th17-related cytokines in systemic lupus erythematosus and rheumatoid arthritis patients. Clinics. 2013 Jun;68(6):766-71.
24. Volin MV, Harlow LA, Woods JM, Campbell PL, Amin MA, Tokuhira M, Koch AE. Treatment with sulfasalazine or sulfapyridine, but not 5-aminosalicylic acid, inhibits basic fibroblast growth factor–induced endothelial cell chemotaxis. Arthritis & Rheumatism: Official Journal of the American College of Rheumatology. 1999 Sep;42(9):1927-35.
25. Sailaja AK. An overall review on rheumatoid arthritis. Journal of current pharma research. 2014;4(2):1138.
26. Rosman Z, Shoenfeld Y, Zandman-Goddard G. Biologic therapy for autoimmune diseases: an update. BMC Med. 2013 Apr;11(1):88.
27. Gómez-Gómez GJ, Masedo Á, Yela C, Martínez-Montiel MP, Casís B. Current stage in inflammatory bowel disease: what is next? World J Gastroenterol. 2015 Oct;21(40): 11282–303.
28. Louie GH, Ward MM. Changes in the rates of joint surgery among patients with rheumatoid arthritis in California, 1983-2007. Ann Rheum Dis. 2010 May;69(5):868–71.
29. Chung KC, Pushman AG. Current concepts in the management of the rheumatoid hand. J Hand Surg Am. 2011 Apr;36(4):736–47.
30. Knut L. Radiosynovectomy in the therapeutic management of arthritis. World J Nucl Med. 2015 Jan-Apr;14(1):10–5.
31. Puddu G, Cipolla M, Cerullo G, Franco V, Giannì E. Which osteotomy for a valgus knee? Int Orthop. 2010 Feb;34(2):239–47.
32. Brooks F, Hariharan K. The rheumatoid forefoot. Curr Rev Musculoskelet Med. 2013 Dec; 6(4):320–7.
33. Halstead JA, Stoten S. Orthopedic Nursing: Caring for Patients with Musculoskeletal Disorders. Bridgewater: Western Schools; 2010.
34. Escott-Stump S. Nutrition and Diagnosis-Related Care. Philadelphia: Lippincott Williams & Wilkins; 2011.
35. González-Álvaro I, Ortiz AM, Seoane IV, García-Vicuña R, Martínez C, Gomariz RP. Biomarkers predicting a need for intensive treatment in patients with early arthritis. Curr Pharm Des. 2015;21(2):170–81.